International Journal of Applied Science and Engineering Review

IJASER

ISSN: 2582-6271

Vol.2 No.4; July-Aug 2021

# EFFECTIVE ROLE OF CRANBERRY AGAINST E. COLI URINARY TRACT ADHESIONS; A REVIEW

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DOI: http://dx.doi.org/10.52267/IJASER.2021.2407

## ABSTRACT

Urinary tract infections have emerged as one of the most notorious bacterial infections in primary health care, and its increasing resistance against most of the available antibiotics makes it prominent among common diseases. Individuals with antibiotic resistance could be on higher risk of getting UTI repeatedly. Therefore, either we need to establish a controlled/prescribed antibiotic use or to find other treatment options, nutritional interventions can play a good role in this regard. A common fruit with a huge number of benefits, Cranberry has been used by North American Indians to treat multiple medicinal conditions including UTI. This review demonstrates the role of cranberry in UTI management by preventing the adhesion of E. coli in the urinary tract. Cranberry appears to work by inhibiting the adhesion of type I and P-fimbriated Escherichia coli to the uroepithelium, thus hinder the colonization and upcoming infections. Adhesion can be averted by 2 ingredients of cranberries: laevulose that prevents binding of type 1 fimbriae and pro-anthocyanidins by preventing p- fimbriae binding. The anti-adherent effect initiates in 2 hours and remains for up to 10 hours after consumption of cranberry. Findings suggest that the use of cranberry can be an effective treatment option along with antibiotics or exclusively for UTI cases.

**KEYWORDS:** Urinary tract infection-UTI, Pro-Anthocyanidins-PAC, Extended Spectrum Beta-Lactamase-ESBL, Escherichia coli-E coli.

## INTRODUCTION

A Urinary tract infection-UTI is known as an infection of any part of urinary system including kidneys, ureters, bladder and urethra caused by several microbes such as Enterococcus faecalis, Escherichia coli, Proteus mirabilis, Klebsiella pneumoniae, and Staphylococcus saprophyticus Foxman (2014) Odoki et al (2019). UTI develops as a result of relationship between urinary pathogen and host, however its pathophysiology requires a multiple step process Barber et al (2016). The initial phase of an infection is the colonization of the peri-urethral tissues, followed by the entrance of bacteria through the urethra and

ISSN: 2582-6271

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the next phase is the attachment of bacteria to the urethra and walls of bladder and started to grow

Flores-Mireles et al (2015) Korbel et al (2017). Pathogen binds to the epithelial surface of the urinary tract. Then it subsequently colonizes and spreads across the mucosa which causes the tissue to be damaged. After the early colonization period the pathogens enter the urinary bladder which results in symptomatic or asymptomatic bacteriuria Luthje and Brauner (2014). Urinary pathogens mostly enter the host by means of three possible routes such as ascending route where pathogen enters the urinary tract by urethra into the bladder Linhares et al (2013). Then comes the hematogenous route where some microorganisms such as Staphylococcus aureus bacteremia or candida fungaemia arise in immunocompromise patients and sometimes the renal parenchyma can be ruptured Glaser and Schaeffer (2015). Finally, in the lymphatic route, bacteria penetrate in the urinary tract with adjoining organ with the help of lymphatics. Izadi et al (2016) The clinical conditions associated with the lymphatic route are retroperitoneal abscesses and chronic bowel infections Pulipati S et al (2017) graphically demonstrated the stages of urinary tract infection figure 1 Pulipati S et al (2017).

The most vulnerable individuals towards UTI are infants, pregnant women, old people, patients with catheters, diabetic patients, patients with multiple sclerosis or acquired HIV and patients with any complicated urologic diseases Foxman (2014). UTIs are almost 50 times more common in grown-up females than males because women have shorter urethras that permit bacteria easily to climb the bladder. The risk factors that put the women to repeated UTIs are antibiotic resistance, menopause, sexual intercourse, bacterial attack and the use of birth control pills Choi et al (2014). Approximately, 1 in 3 women have affected 1 time by UTI by 24 years and 50% females encounter UTI one time in their lifetime and needs antibiotic treatment Zhao et al (2020). Unnecessary or prolonged use of antibiotics as well as self-medication has brought antibiotic resistance as a big challenge for the healthcare system Geerlings et al (2013). Therefore, non-antibiotic methods are gaining much interest to prevent UTI especially for mild cases Suskind et al (2016).

Cranberry: A group of shrubs “Vaccinium macrocarpon or cranberry” known for having multiple nutritional benefits have also been used by ancient Americans for the treatment of various illnesses such as fever, blood disorders, liver problems, and stomach diseases Zhao et al (2020). Cranberry juice enriched with Omega-3 helps in the management of diabetes, hypertension, and obesity by modulating their commonly involved factors like total cholesterol, LDL cholesterol and insulin resistance Zare et al (2018) Kowalska and Olejnik (2016). Polyphenols present in cranberry have effective role as anti-inflammatory, anti-allergic, antifungal, antiviral, and antihypertensive properties, and minimize the chances of metabolic diseases Oszamianski et al (2018). In addition, Cranberry, or cranberry juice help to reduce the symptoms of UTI by reducing the inflammation as a natural defense against bacterial attack Smarsinghe et al (2019). Cranberries contain water more than 80% and almost 10%

International Journal of Applied Science and Engineering Review

IJASER

ISSN: 2582-6271

Vol.2 No.4; July-Aug 2021

carbohydrates, ingredients/components of cranberry can be seen in figure 2 Geerlings et al (2013).

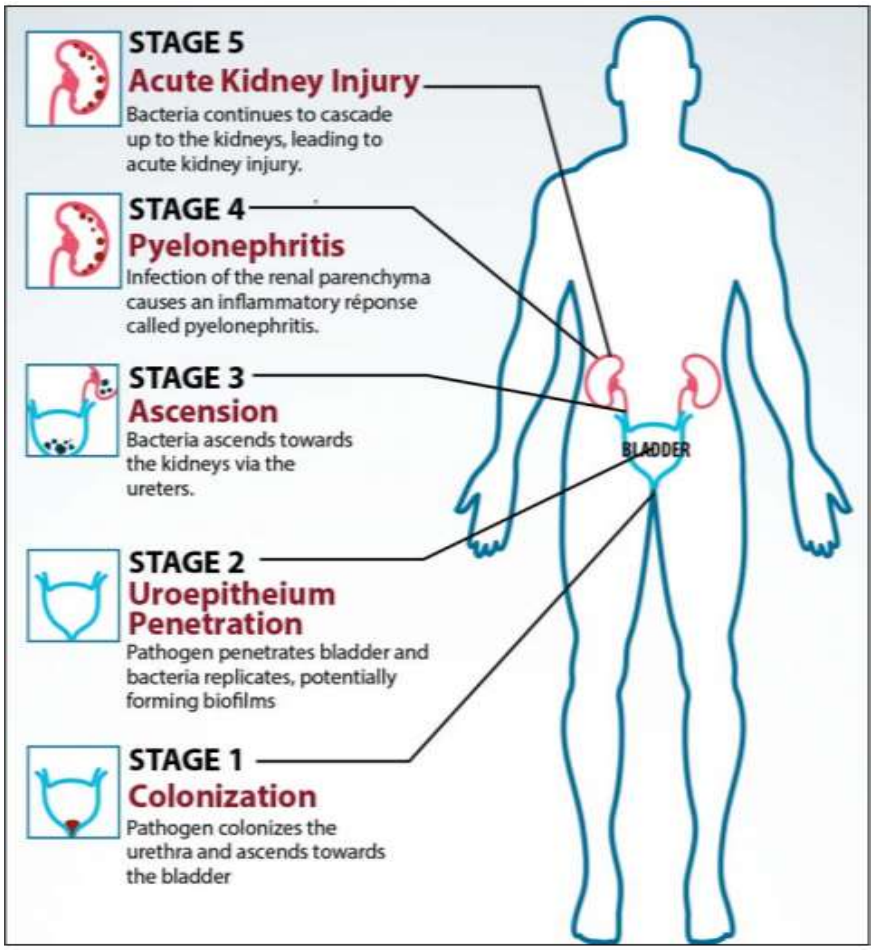


**Figure 1 Different stages of urinary tract infection [1].**

International Journal of Applied Science and Engineering Review

IJASER

ISSN: 2582-6271

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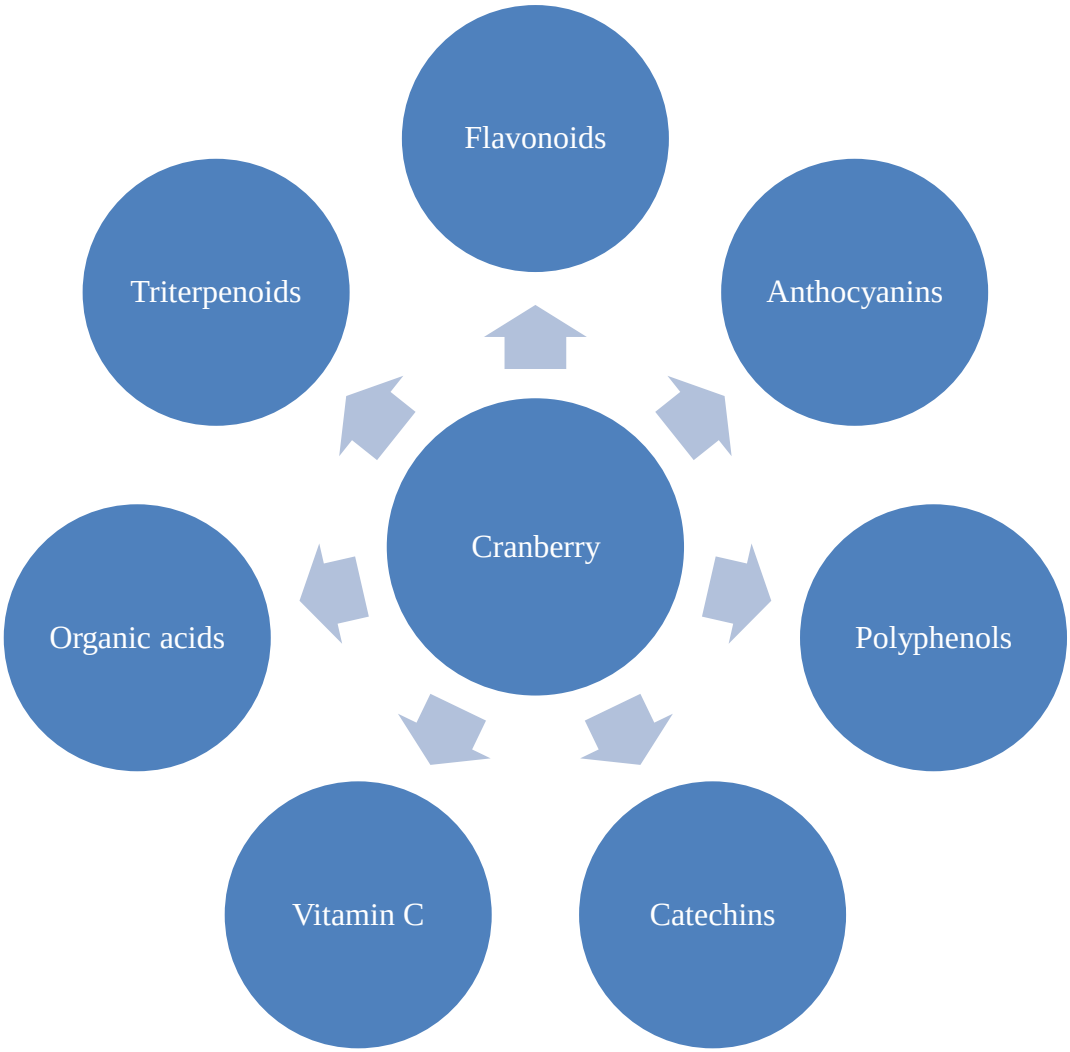


**Figure 2 Ingredients/components of cranberry.**

The organic acids present are malic, citric and quinic acids, with very little quantity of benzoic acid and glucuronic acids Zhao et al (2020). Other compounds like anthocyanidins and Pro-Anthocyanidins-PAC are only found in vaccinium berries that provide natural protection against microorganisms. Cranberries can be consumed as fresh berries, whole berries, juices (usually 10-25% pure juice), powdered form and capsules Vostalova et al (2015)

Cranberry against E. coli: Cranberry contain citric acid, malic acid and quinic acid with small amount of benzoic acid, ascorbic acid and glucuronic acids with antibacterial properties and acidify the urine by

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excreting large amount of hippuric acid Jabin et al (2017). Pathogenic E. coli attaches to epithelia in the lower urinary tract and towards renal tubular epithelial cells in the kidney by the connection through P-fimbriae and other aspects. Cross connection of toll-like receptor 4 with glycol-sphingolipid receptors decrease the lack of cluster-of-differentiation 14 in these epithelia. Ligation of the lipopolysaccharide's receptor complex creates local countenance of chemokine ligand 2/Interleukin 8. The adjacent endothelial cells of peritubular capillaries get activated and up regulated. Local neutrophil conscription, renal abscess formation and leukocyturia are followed with linkage molecules and chemokines Sujata et al (2015).

There are two compounds that are responsible to block attachment of E. coli in UTI patients. First is fructose, which restrains mannose-sensitive fimbrial adhesions and the second one is a high atomic weight compound that restrains the mannose-resistant adhesions of pathogenic E. coli. Almost all fruit juices contain fructose, but only Vaccinium berries (i.e., cranberries and blueberries) contain this extraordinary second compound, later named as "pro-anthocyanidin." Interestingly, pro-anthocyanidin is strongly effective against mannose-resistant adhesins that is produced by E. coli present in Urine samples but show very light effect against E. coli present in fecal samples Maki et al (2016). The pro-anthocyanidins has an active down regulation action on the aptness, virulence, and resistance of antibiotic in the Extended Spectrum Beta-Lactamase (ESBL) producing strain of E. coli CTX-M 15 Teles et al (2013). Singh et al. observed that proanthocyanins in cranberry can significantly reduce the bacterial adhesion, maintain urinary PH, and ultimately can reduce the chances of UTI Singh et al (2016). In another attempt, it was observed that cranberry juices & pills lower the risk for UTI as compared to the placebos Santillo and Lowe (2007) and Regular consumption of cranberry juice was also found effective in patients with UTI despite the presence of antibiotic-resistance Zhao et al (2020). The metabolites in cranberry have effective role in preventing the adherence of bacterial pathogen to urinary tract epithelium, colonization of bacteria and occurrence of urinary tract infection Thimoto et al (2019). The anti-adhesive property of cranberries probably helps to prevent UTI in 2 ways: first, it directly prevents E. coli from adhering to uroepithelial cells; and second, it chooses less invasive bacterial strains in the stool. The anti-adherent effect initiates in 2 hours and remains for up to 10 hours after consuming Linhares et al (2013). Altogether, these properties of cranberry contribute to the prevention and elimination of E. coli by averting its adhesion to the host epithelium.

International Journal of Applied Science and Engineering Review

IJASER

ISSN: 2582-6271

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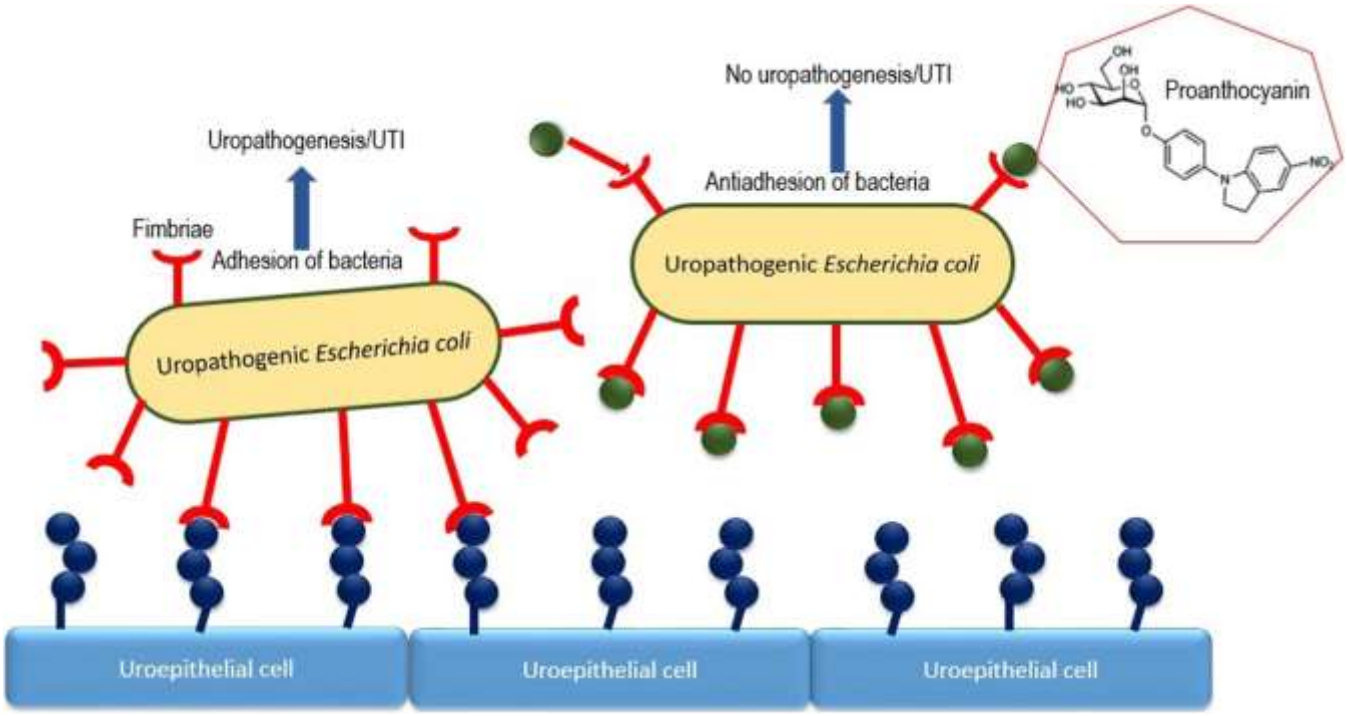


**Figure 3 Proanthocyanins as inhibitors of P-fimbriae during bacterial uroepithelial attachment Das(2020)**

Gut microbiota is known to be the beneficial bacteria residing in different origins of the body (most prominently in intestine) and are associated with metabolism of cranberry polyphenol. Cranberry polyphenols are involved in prevention of pathogen's colonization in intestine Glaser and Schaeffer (2015). Cranberry polyphenol (flavonoids & phenolic acid) and gut bacteria have a "2-way interaction" against UTI. Pyelonephritis and renal dysfunction can contribute to further progression of this process. The unique virulence factors living on the membrane of pathogens are responsible for bacteria resisting the host defense mechanism Poat et al (2021). Recently, bacterial adhesin and their linked epithelial binding sites have been recognized. The adhesin proteins are known as pilus and fimbriae Barbosa et al (2011). Attachment of bacteria is achieved by lectins attachment discovered by target cells of this pilus of carbs of host cell. Pili are tiny strands which allow binding bacteria to cells; sometimes some protein is mannose-resistant or mannose-sensitive. Bacterial binding to urothelium is enabled by the mannose-sensitive pili, termed type 1 pili; the pilus are hindered due to fructose Shin (2014). The present theory is that cranberries function mainly by prohibiting the urothelium from adhering to type 1 pilliand Pap strains. Bacteria can not affect the surface of mucosa without attachment Van Duynhoven et al (2014). Shin et al. explained that the binding is affected by 2 ingredients of cranberries laevulose, that prevents

ISSN: 2582-6271

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binding of type 1 fimbria and pro-anthocyanidins, which prevents p-filli binding. A receptor ligand attachment is supported by hydrophobic nature, that occurs as attachment of a protein's bacterial fimbriae edges to urinary tract epithelium layer. One underlying strategy is that the cranberry metabolites such as propionic acid, hippuric acid and catechol-O-sulphate that profitably suppresses the adhesion that function like binding site analogues via connecting the fimbriae edges to target tissues Zhou et al (2011). Cranberry action decreases p-filli function in Escherichia coli by altering surface compounds composition. Vaccinium Oxycoccus (cranberries) reduces the infectivity Strains of Escherichia coli. More studies proved that extract of cranberries has many different effects on p-filli. The route from digestion to urinary system is not clearly mentioned. Few studies explained that, in-vivo proanthocyanins were not active because of the large particles that cause difficulty in GIT absorption Flores-Mireles et al (2015).

In human colorectal adenocarcinoma cell, the structure of proanthocyanins is porous. Regarding their ability to get absorbed, some studies confirmed human excretion of proanthocyanin. In the urinary tract and large intestine, there are chances that if proanthocyanins is active, some strains may bind, and E. coli fails to bind. By that means, giving them non sticking agents before they localize in the urinary tract. Types of cranberry stop the growth of bacteria in large intestine Hussien et al (2015). After consuming twelve hundred milli grams of dry juice of cranberry, there were decreased level of anthocyanin and pro anthocyanin in urine output. As experimenting in the studies, it was concluded that only 0.078 of five percent of human anthocyanin were excreted out after consuming the juice of cranberry Shin (2014). After three to six hours of juice intake, high concentration of anthocyanins was observed and in first twelve hours the urine output was completed Maki et al (2016). Many investigations mentioned E. coli and its strains, but in in-vitro study shows hindrance of attaching with gram negative proteobacteria, pseudomonas aeruginosa, enterococcus, staphylococcus, salmonella and klebsiella Vostalovia et al (2015). However, it is not proved that the process of absorption, metabolism, and excretion of juice of cranberries in urine output is not effective from protecting any bacterial growth.

## CONCLUSION

During the era of increasing antibiotic resistance, there is an urgently need to find more options to treat bacterial infections. A lot of research is being conducted to achieve this goal including probiotic studies, bacteriophages, peptides, biopolymers, and more. However, nutritional interventions are also gaining interest in this regard. Numerous herbs, fruits, vegetables, dairy products, and meats are being studied for their beneficial uses in replacing the medicines. Cranberry or its nutrients can be a potential treatment option for the urinary tract infection. It has a plausibility factor which contemporaneous inhibits the P-fimbriated Escherichia coli strains adhesion. Further studies can be conducted to explore

the application of cranberry or its extracts against different medical conditions which involve pathogen adhesion and inflammation.

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ISSN: 2582-6271

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